



MicroRNAs: fundamental regulators of gene expression in major affective disorders and suicidal behavior?

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INTRODUCTION

Major affective disorders are one of the foremost causes of morbidity worldwide; such disabling conditions are also frequently associated with suicidal behavior (Innamorati et al., 2011; Gonda et al., 2012; Serafini et al., 2012). Although many psychopharmacological agents are currently available, in particular for the treatment of major depressive disorder (MDD) (Serafini et al., 2013), our knowledge concerning the molecular and cellular mechanisms underlying this complex condition is still limited. Indeed, even minor alterations in the expression of genes regulating neural and structural plasticity may be crucial to understanding the pathogenesis of major affective disorders (Dwivedi et al., 2009a,b; Serafini et al., 2011, 2012).

MiRNAs are gene expression regulators critically affecting brain development that have been investigated as potential biomarkers for the diagnosis, management, treatment, and progression of neuropsychiatric disorders (Machado-Vieira et al., 2010; Saugstad, 2010; Dwivedi, 2011). Several facets of miRNA expression alterations are currently under investigation to gain insight into the pathology of neuronal disorders (Hansen et al., 2007; Lopez et al., 2013): miRNA expression alterations in pathophysiological models of disease (Ziu et al., 2011; Brandenburger et al., 2012); miRNA expression alterations in the blood of patients, most of which represent further downstream or compensatory effects (Schipper et al., 2007; Gallego et al., 2012); and miRNAs

and their effectors acting as targets for the action of psychoactive drugs such as antidepressants and mood stabilizers (Zhou et al., 2009; Baudry et al., 2010; Oved et al., 2012).

Several miRNAs have emerged as potential mediators of depressive pathophysiology. The existence of polymorphisms in pre-miR-30e (Xu et al., 2010) and pre-miR-182 (Saus et al., 2010) has been associated with an increased risk of major depression. Depressive behavioral responses have been induced by miR-16 up-regulation in the raphe nuclei and hippocampus, with the latter associated with subsequent down-regulation of BDNF (Bai et al., 2012). MiR-16 down-regulation within the locus coeruleus was also induced in depressive mouse models (Launay et al., 2011). Smalheiser et al. (2012) investigated the expression of miRNAs in the prefrontal cortex (specifically in Brodmann Area 9) of 18 antidepressant-free depressed suicide victims, and 17 well-matched non-psychiatric controls, whose information was collected using the psychological autopsy method. In this study, global miRNA expression was significantly down-regulated by 17%, and 24 miRNAs were down-regulated by at least 30%. The authors also found significant down-regulation in an extensive inter-connected network of 21 miRNAs involved in cellular growth and differentiation. Notably, both the global decrease of miRNA expression, as well as its decreased variability, are consistent with hypo-activation of the frontal cortex

in depressed subjects. Interestingly, the noted miRNAs have been suggested to be down-regulated in the frontal cortex of rats treated with corticosterone, and therefore, might be crucial in regulating stress-mediated miRNA expression in depressed subjects (Dwivedi et al., unpublished data). Hence, alterations in miRNA expression may be a fundamental event underlying gene network reorganization associated with major depression.

Nevertheless, a comprehensive understanding of miRNA networks dysregulated in major depression and induced by antidepressant medications as a function of brain region is currently unknown (Mouillet-Richard et al., 2012). It is also generally poorly understood how miRNA regulation affects cellular signaling networks in these biological processes. Here we provide an overview and critical review of the published work, particularly examining the role of miR-185 in major depression and suicidal behavior.

THE CHALLENGES OF miRNA:mRNA TARGET PREDICTION IN MODELING PATHOLOGY

Expression profiling and RNA sequencing of miRNAs have increased our understanding of which miRNAs are present in specific tissues, and how they may change under pathological conditions (Oved et al., 2012). However, once identified, linking a miRNA to its mRNA targets can be a challenging task, and the authenticity of functional miRNA:mRNA target pairs should be validated. A very small fraction

of software-predicted miRNA targets are validated *in vivo*. As suggested by Koppers et al. (2011), only a subset of predicted targets are consistently reduced in phenotypes that overexpress some miRNAs. Validation could be provided by showing a direct interaction between the miRNA and mRNA target. Further, miRNA silencing, overexpression, and luciferase reporter based assays are commonly used as supporting evidence for a functional interaction (Kuhn et al., 2008).

Many databases for miRNA target prediction have been created using an array of interrogation approaches. Considering varying degrees of sequence similarity, conservation, site accessibility, and variation in the targeted regions of the mRNA, the numerous databases can provide a surprising level of divergent results. This divergence speaks to the difficulty that scientists have had in developing a clear and concise set of rules underlying miRNA:mRNA interaction: clearly target prediction software should only be viewed as a tool to guide bench science.

Table 1 Provides a summary of current miRNA target prediction software that may be used to guide *in silico* investigations into miRNA and their putative targets. The analytical paradigms for each database are described as well as advantages of each mode of inquiry.

miR-185: A ROLE IN MAJOR AFFECTIVE DISORDERS AND SUICIDAL BEHAVIOR?

Preliminary studies have suggested the importance of miR-185 and miR-491-3p in the pathogenesis of major depression and suicidal behavior. miR-185 is expressed in several brain regions such as the hippocampus and cortex, predominantly in synapses (Lugli et al., 2008; Xu et al., 2013). Earls et al. (2012) reported that miR-185 regulates cognitive and psychiatric symptoms of patients with the 22q11 deletion syndrome. Recently, Xu et al. (2013) suggested that miR185 controls the expression of Golgi-apparatus related genes including a new inhibitor of neuronal maturation. In particular, a reduction of miR-185 altered dendritic and spine development resulting in structural alterations of the hippocampus.

With respect to MDD and suicidality, miR-185 was shown to be upregulated in

patients who completed suicide (Maussion et al., 2012). These increases in expression were correlated with reduced TrkB-T1, a truncated TrkB transcript whose downregulation has been associated with suicide (Ernst et al., 2009). The downregulation of TrkB-T1 was associated with suicidal behavior in a sample of 38 suicide completers (60.5% having been previously diagnosed with MDD). Of note, five putative binding sites for miR-185 were found in the 3' UTR of TrkB-T1 (using an *in silico* investigation). Array findings were confirmed with RT-PCR investigation and three of the five potential binding sites for miR-185 in the TrkB-T1 3' UTR were demonstrated to be functional by luciferase assay. The authors did not find any confounding effect of age, pH, PMI, or suicide method. Through Pearson correlation and subsequent *in vitro* functional analyses (using silencing or exogenous expression of miR-185), TrkB-T1 levels and hsa-miR-185 levels were reported to be inversely correlated.

A few notes of caution should be mentioned with regard to the Maussion et al. (2012) study. The authors acknowledge that the underlying mechanism of increased miR-185 expression remains unclear. The study used HEK293 cells that yielded TrkB-T1 expression levels that were 10-fold greater than neuronal cell lines. Furthermore, RNA binding proteins, such as ELAVL1 or PABPC1, may be expressed in HEK293 cells (Drury et al., 2010) and potentially bind TrkB mRNA (Jain et al., 2011). Therefore, despite disproportionate increases in TrkB-T1 expression, the functional effect of hsa-miR-185 on TrkB-T1 observed in HEK293 cells might have been attenuated by the expression of these genes and their binding activity (George and Tenenbaum, 2006). Further, the study is limited by the small sample size and the negative findings in other brain regions, such as the cerebellum. Indeed, presumably only a limited part of the total variability in miRNAs that might regulate TrkB-T1 has been identified.

Of note, the subjects of the Maussion et al. (2012) study were not assessed for microduplications in the 22q11.2 region. This is of potential interest because the miR-185 locus maps to the 22q11.2 region, which has been associated with mood

disorders such as depression and anxiety (Jolin et al., 2012; Weisfeld-Adams et al., 2012; Tang et al., 2013). Deletions of this region have also been consistently associated with schizophrenia (Karayiorgou et al., 2010) whereas duplications have been found in patients with autism (Lo-Castro et al., 2009). Alterations in the 22q11.2 region are also associated with morphological alterations in dendritic spines at glutamatergic synapses (Mukai et al., 2008), and abnormal maturation of miRNAs (Stark et al., 2008). Fénelon et al. (2013) have suggested that mice with a 22q11.2 microdeletion show significant alterations in high-frequency synaptic transmission, short- and long-term plasticity, and dendritic spine stability. The authors reported that variation in synaptic plasticity occurs by subtle changes in neuronal density and a reduction in inhibitory neuron. All of these alterations in neuronal function could play critical roles in depressive pathophysiology.

UNDERSTANDING THE LIMITATIONS OF STUDIES EXAMINING THE ROLE OF miRNAs IN MAJOR AFFECTIVE DISORDERS

Since the first detection in *Caenorhabditis elegans* in 1993 (Lee et al., 1993), small interfering RNAs have raised great interest among neurobiologists for their potential role in neuropathological regulation. In line with this notion, large-scale analyses on post-mortem brains, as well as investigations in animal models of depression, have evaluated the impact of psychoactive medications on global miRNA expression. Transcriptome studies are now commonly used as a starting point to investigate the association between dysregulated miRNAs and major affective disorders. However, there are a number of conflicting studies with regard to the magnitude and direction of biologically-relevant miRNA expression changes in psychiatric disorders (Perkins et al., 2007; Beveridge et al., 2010). This could be due to tissue-specific variations in expression levels as well as heterogeneity in quantification and normalization procedures (Belzeaux et al., 2012). Furthermore, some studies on miRNAs and depression were conducted in peripheral blood despite uncertainties regarding how

Table 1 | Comprehensive list of miRNA target databases and software.

Databases for miRNAs and their target gene associations	Description	Release date of the last version	Web link	Publication
DIANA-microT	This is an algorithm specifically trained on a positive and negative set of miRNA Recognition Elements (MREs) located in both the 3'-UTR and CDS regions. This new server detects miRNA targets in mRNA sequences of <i>Mus musculus</i> , <i>Drosophila melanogaster</i> , <i>C.elegans</i> , and <i>Homo sapiens</i> . It also provides hyperlinks to on-line servers such as iHOP and expression data for the selected miRNAs in tissues and cell lines. Each gene is weighted considering conserved as well as non-conserved sites. Furthermore, a signal to noise ratio is applied for each interaction in order to estimate the number of false positives.	Jul, 2012 (version 5.0)	http://www.microna.gr/microT-CDS	Reczko et al. (2012)
MicroCosm	This is a miRNA target database that has been developed by Enright lab at EMBL-EBI. MicroCosm Targets includes computationally predicted microRNA targets for many species and is based on a dynamic program to search for maximal local complementarity alignments. The miRNA sequences are derived by the miRBase Sequence database and most genomic sequence from Ensembl. MicroCosm uses the miRanda algorithm that is one of the first miRNA target prediction algorithms.	Ago, 2010 (version v5)	http://www.ebi.ac.uk/enright-srv/microcosm/htdocs/targets/v5/	Griffiths-Jones et al. (2008)
miRanda and microRNA.org	It includes both software (miRanda) and a miRNA database (microRNA.org). This algorithm uses a score to rank the predictions according to a weighted sum based on matches, mismatches, and G:U wobbles. The newest version of MiRanda is also called mirSVR, it also considers a conservation measure based on the PhastCons conservation score.	Ago, 2010	http://www.microna.org/microna/home.do	Betel et al. (2008)
miRDB	All the targets are predicted by the bioinformatics tool MirTarget2, which analyzes thousands of genes impacted by miRNAs with an SVM learning machine. MiRDB includes predicted miRNA targets from the following organisms: humans, mouse, rat, dog, and chicken. MiRNA targets are predicted using common features associated with miRNA target binding. The positive and negative datasets for training consist of many negative and positive interactions, respectively.	Jan, 2012 (version 4.0)	http://mirdb.org/miRDB/	Wang and El Naqa (2008)
miRecords	This is an integrated microRNA target database for miRNA-target interactions. It provides miRNA-target relationships predicted by multiple target algorithms, such as Targetscan, PicTar, miRanda, PITA, and RNA22. It provides a large manually curated database including experimentally validated miRNA-target interactions with systematic documentation of experimental support for each interaction. It is expected to serve for experimental miRNA researchers, and informatics scientists.	Apr, 2013	http://mirecords.umn.edu/miRecords/	Xiao et al. (2009)
miRGator	This is an algorithm integrating the target prediction, functional analysis, gene expression data, and genome annotation. MiRNA function is inferred from the list of target genes predicted by other databases (miRanda, PicTar, and TargetScanS). For the expression analysis, miRGator integrates public expression findings of miRNAs with those of mRNAs and proteins.	Dic, 2012 (version 3.0)	http://genome.ewha.ac.kr/miRGator/miRGator.html	Nam et al. (2008)

(Continued)

Table 1 | Continued

Databases for miRNAs and their target gene associations	Description	Release date of the last version	Web link	Publication
miRGen++	miRGen is an integrated database including positional relationships between animal miRNAs and genomic annotation sets as well as animal miRNA targets, according to combinations of widely used target prediction programs. It provides comprehensive information about the position of human and mouse microRNA coding transcripts and their regulation by transcription factors.	Jan, 2007 (version 3)	http://www.diana.pcbi.upenn.edu/miRGen.html	Megraw et al. (2006)
MiRNAMap	This is an integrated database aimed to identify experimentally verified miRNA target genes in human, mouse, rat, and other metazoan genomes. MiRNA targets in 3'-UTR of genes and the miRNA targets were identified using the following computational tools: miRanda, RNAhybrid, and TargetScan. The putative miRNA targets are adequately filtered in order to reduce the false positive prediction rate of miRNA target sites.	Jul, 2007 (version 2.0)	http://mirnamap.mbc.nctu.edu.tw/	Hsu et al. (2008)
miRTarBase	This is an experimentally verified miRNA target base, including more than 3000 miRNA–target interactions collected by manually surveying pertinent literature. Generally, the collected miRNA–target interactions are validated experimentally based on reporter assays, western blot, or microarray experiments with overexpression or knockdown of miRNAs.	Jul, 2013 (version 4.3)	http://miRTarBase.mbc.nctu.edu.tw/	Hsu et al. (2011)
miRWalk	miRWalk is a comprehensive database providing information on miRNAs from human, and mouse, including their predicted and validated binding sites for their target genes. MiRWalk considers a newly developed algorithm aimed at creating the predicted miRNA binding sites on the complete sequences of all known genes of the human, mouse, and rat genomes. It provides predicted miRNA binding sites on genes associated with over 400 human biological pathways and over 2300 OMIM disorders. It also includes information on proteins known to be implicated in miRNA processing.	Mar, 2011	http://www.umm.uni-heidelberg.de/apps/zmf/mirwalk/	Dweep et al. (2011)
PicTar	PicTar is used for the identification and prediction of miRNA targets by combining multiple miRNAs or targets. This website provides details concerning: miRNA target predictions in vertebrates; miRNA target predictions in seven <i>Drosophila</i> species; miRNA targets in three nematode species; human miRNA targets that are not conserved but co-expressed (e.g., both the miRNA and mRNA that are expressed in the same tissue).	Mar, 2007	http://pictar.mdc-berlin.de/	Lall et al. (2006)
PITA	This algorithm predicts miRNA targets taking into account not only the specific duplex interaction information, but also the accessibility (the difference between the minimum free energy of the whole complex and the initial energy of a short mRNA region near the site) to the site in the mRNA. Several restrictions may be applied to reduce the set of resulting predictions.	Ago, 2008 (version 6)	http://genie.weizmann.ac.il/pubs/mir07/mir07_data.html	Kertesz et al. (2007)

(Continued)

Table 1 | Continued

Databases for miRNAs and their target gene associations	Description	Release date of the last version	Web link	Publication
RNA22	It is a pattern-based strategy aimed to identify the candidate targets. A Markov chain is used to identify those patterns which are hypothesized to identify areas where the most statistically significant patterns map (target islands). The target islands are subsequently paired with miRNAs.	May, 2008 (version 1.1.2)	http://cbcsrv.watson.ibm.com/rna22.html	Miranda et al. (2006)
RNAhybrid	This algorithm provides a flexible software for predicting miRNA targets. It is a tool that finds the minimum free energy not only for short sequences as most of the mentioned algorithms, but also for the entire miRNA–mRNA. The analysis is carried out by hybridizing the short sequence to the best fitting part of the long sequence. Several restrictions like the number of unpaired bases and free energy allowed may be applied to reduce the set of resulting predictions.	Jul, 2013 (version 2.1.1–2)	http://bibiserv.techfak.uni-bielefeld.de/rnahybrid/	Kruger and Rehmsmeier (2006)
StarBase	This algorithm provides a public platform developed to facilitate the comprehensive exploration of miRNA–target interaction from CLIP-Seq (HITS-CLIP, PAR-CLIP) and degradome sequencing (PARE) data from the following organisms: human, mouse, <i>Caenorhabditis elegans</i> , <i>Arabidopsis thaliana</i> , <i>Oryza sativa</i> , and <i>Vitis vinifera</i> . It also provides intersections of multiple target predictions, such as Targetscan, PicTar, miRanda, PITA, RNA22, and miRSVR.	Sep, 2011 (version 2.1)	http://starbase.sysu.edu.cn/	Yang et al. (2011)
TarBase	This is a large available target database including more than 65,000 miRNA–gene interactions. It includes targets derived from both microarrays and proteomics. It is linked to other databases such as Ensembl, Uniprot, RefSeq, and DIANA-microT enabling extension of each validated interaction with <i>in silico</i> predicted information.	Jan, 2009 (version 6.0)	http://microrna.gr/tarbase/	Vergoulis et al. (2012)
TargetRank	TargetRank scores the seed matches in a UTR relative to a given siRNA or miRNA and then calculates an overall score for the mRNA as a whole by summing the scores for all seed matches present in the 3' UTR. Only targets with scores above 0.2 are reported. The relative ranking given by TargetRank may be considered more useful than the score itself.	Mar, 2006	http://genes.mit.edu/targetrank/	Nielsen et al. (2007)
TargetScan	This algorithm requires the seed complementary at least for 6 nt and considers the different seed types that have been defined using a specific hierarchy. It predicts microRNA targets from conserved UTR sequences by searching for the presence of conserved and non-conserved sites matching the seed region of each miRNA. In the last version of this algorithm, a multiple linear regression trained on 74 filtered datasets has been used to integrate determinants.	Mar, 2012 (version 6.1)	http://www.targetscan.org/	Friedman et al. (2009)

closely changes in peripheral miRNA expression reflect modifications in the central nervous system (e.g., Bocchio-Chiavetto et al., 2013). It is also worth noting that, “control” RNAs commonly used to normalize miRNA data (U6,

U44, and U48) are very sensitive to post-mortem decay (Sadikovic et al., 2011) and thus, should be carefully matched among groups to prevent the emergence of artifactual shifts in miRNA expression. Finally, neuronal shrinkage, loss of glial

cells, or loss of dendritic spines may also contribute to changes in miRNA levels. Clearly, changes in tissue composition or cellular compartments should be carefully taken into account when examining the available studies.

CONCLUSION

Our understanding of the molecular mechanisms underlying major affective disorders may be significantly enriched by the knowledge of miRNAs' mechanisms of action. MiRNA targets are critically involved in stress-related disorders, neuroplasticity, and neurodevelopmental disorders (Rogaev, 2005). Given that miRNAs have been hypothesized to modulate ~50% of protein-coding genes and hundreds of mRNAs (Krol et al., 2010), a new level of complexity regarding gene expression has emerged. The entire miRNA context (both mRNA networks and their cellular environments) should be critically investigated when interpreting the effects of changes in miRNA levels. Much remains to be examined in order to translate these investigations into novel therapeutics for the treatment of psychiatric conditions.

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